Neurosurgical Focus

Prognostic variables in surgery for skull base meningiomas

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The authors have retrospectively analyzed selected surgical and pathological observations made among a group of 20 patients harboring recurrent cranial base meningiomas in an attempt to reveal which factors may be important in predicting tumor recurrence. This cohort was compared with a group of 34 patients with cranial base meningiomas that underwent primary resection and in whom tumor recurrence has not been demonstrated over a median follow-up period of 33 months. Features analyzed included brain, cranial nerve, carotid artery, or muscle invasion as well as tumor cellularity, nucleolar prominence, cellular pleomorphism, and percentage of cells staining positive for the Ki-67 antigen. As expected, increased cellularity and tumor necrosis were relatively more prevalent in recurrent tumors. With regard to tumor type, atypical and anaplastic tumors were more common in the group of patients with recurrent tumor compared with the primary group ($p < 0.02$). As expected, increased cellularity was relatively more prominent in recurrent tumors. Invasion of muscle and bone (72%) was more frequently associated with recurrent tumors, suggesting that these characteristics may be important features of recurrent skull base meningiomas.

Key Words * skull base * meningioma * prognostic factor

The identification of predictors of recurrence of skull base meningiomas remains an important area of study in neurosurgery. The subject becomes more relevant as operative techniques improve and expand the number of tumors that are amenable to surgical resection.[2,12,13] Additionally, the increasing availability of alternative therapies, such as radiosurgery, makes an objective assessment of the efficacy of surgical resection more important.[10,17,24,26]

Skull base meningiomas account for 25 to 30% of all meningiomas, yet their rate of recurrence is disproportionally high at 40 to 50%.[14] This compares to an overall meningioma rate of recurrence of 10 to 30%.[19] Although some of this high rate of recurrence may be attributed to the difficulty of exposing and adequately removing these lesions, it is not clear if factors other than tumor location might be identified that could characterize these lesions. The purpose of this study was to examine standard clinical, surgical, and pathological parameters in patients with recurrent and nonrecurrent skull base meningiomas treated at our institution to see if we could identify factors that might be associated with tumor recurrence.

CLINICAL MATERIAL AND METHODS

Patient Selection

A total of 54 patients (40 women/14 men) with skull base meningiomas were studied retrospectively. Each patient underwent surgery performed by a member of the faculty of the Department of Neurosurgery at the University of Southern California University Hospital between August 1991 and August 1994. This is a series of patients with skull base meningiomas with progressing clinical signs and symptomatology in whom careful follow up was obtained. However, no attempt was made to match these two groups of patients with regard to any variable. All the pathological slides were interpreted by a single neuropathologist (D.R.H.). Thirty-four of these patients (27 women/seven men) had nonrecurrent, or primary, meningiomas and the remaining 20 patients (13 women/seven men) had recurrent tumors. The median age of the patients with nonrecurrent tumors was 54 years, and the median age of the patients with recurrent tumors was 51 years.

Tumor Location

The tumor locations were broadly categorized as existing in one of the following sites and stratified by nonrecurrence/recurrence: orbital region (9 patients), olfactory groove/subfrontal/planum sphenoidale (6 patients), parasellar (8 patients), cavernous sinus (12 patients), sphenoid wing (6 patients), and petroclival/petrous apex (13 patients) (Table 1).

TABLE 1
TUMOR LOCATIONS STRATIFIED BY RECURRENCE/NONRECURRENCE

Region	Primary	Recurrent	Totals
orbital	3	6	9
olfactory groove/sub-frontal/planum sphenoidale	4	2	6
parasellar	6	2	8
cavernous sinus	7	5	12
sphenoid wing	4	2	6
petroclival/petrous apex	10	3	13
totals	34	20	54

Clinical Signs and Symptoms

Several clinical signs and symptoms were evaluated in each patient. These included duration of symptoms (in months), visual acuity/field defects, cranial nerve three, four, and six deficits, other cranial nerve deficits, motor or sensory deficits, headaches, proptosis, and alterations in cognition. A clinical sign or symptom was only reported for a given tumor if it represented a new finding in that patient. Therefore, if a patient initially presented with visual acuity defects that did not improve following the initial surgery, the defect would not be noted if the tumor recurred.

Surgical and Pathological Observations

A number of surgical observations were also tabulated. These included muscle or bone invasion, cranial nerve invasion, cavernous sinus invasion, carotid artery encasement, and gross-total tumor resection.[7,8] A gross-total resection was defined as a Simpson Grade I or II and a subtotal resection was defined as a Simpson Grade III, IV, or V.[23] Muscle, bone, and cranial nerve invasion, if observed surgically, had to be verified pathologically.

The tumors were classified according to the World Health Organization classification[5] (typical,

atypical, or anaplastic) for central nervous system tumor malignancy. These included the presence of mitotic figures, increased cellularity, brain invasion, nuclear pleomorphism, tumor necrosis, and nucleolar prominence.[5,11] The Ki-67 labeling index[3,22] using MIB-1 antibodies was analyzed in 27 of 34 primary tumors and 12 of 20 recurrent tumors. This value was determined by calculating the mean labeling index for the five microscopic fields with the highest labeling indices.

Statistical Analysis

The Student's t-test was used to compare the data from the recurrent and nonrecurrent groups. A probability value of less than 0.05 was considered significant.

TABLE 2
CLINICAL SIGNS AND SYMPTOMS EVALUATED IN PATIENTS WITH PRIMARY AND RECURRENT MENINGIOMAS

Parameter	Primary	Recurrent	p Value
duration of symptoms	38 months	4.6 months	<0.05
visual acuity/field deficits	38 %	50 %	NS*
cranial nerve III, IV, VI	41 %	25 %	NS
other cranial nerve deficits	29 %	25 %	NS
motor or sensory deficits	32 %	25 %	NS
headaches	18 %	15 %	NS
proptosis	21 %	35 %	NS
alteration in cognition	15 %	15 %	NS

* NS = not significant.

RESULTS

Of the clinical signs and symptoms that were evaulated (Table 2), only the duration of symptoms was noted to be statistically significant between the groups with primary and recurrent meningioma. In the group with primary meningiomas, the average duration of symptoms was 38 months, whereas in the group whose tumors recurred, the average duration of symptoms was 4.6 months ($p < 0.05$). Visual acuity or visual field defects were present in 38% of patients with primary tumors and 50% of those with recurrent tumors. Involvement of cranial nerves three, four, and six was more common in nonrecurrent tumors (41%) versus recurrent tumors (25%). Proptosis was more common in those patients with recurrent tumors (35%) versus those with primary tumors (21%). These differences, however, were not statistically significant. In the remainder of the parameters tested (other cranial nerve deficits, motor or sensory deficits, and headaches) there was little difference in the incidence between patients with primary and those with recurrent tumors.

TABLE 3
SURGICAL OBSERVATIONS IN PATIENTS WITH PRIMARY AND RECURRENT MENINGIOMA

Observation	Primary	Recurrent	p Value
muscle or bone invasion	38 %	72 %	<0.05
cranial nerve invasion	35 %	33 %	NS
cavernous sinus invasion	38 %	39 %	NS
carotid artery encasement	26 %	39 %	NS
gross-total resection	21 %	22 %	NS

In the category of surgical observations (Table 3), muscle or bone invasion was noted to be significantly

more common in recurrent (72%) versus primary (38%) tumors ($p < 0.02$). Carotid artery encasement was relatively more common in recurrent tumors (39%) versus nonrecurrent lesions (26%). For the remainder of the parameters tested (cranial nerve invasion, cavernous sinus invasion, and incidence of gross-total resection) there was virtually no difference between the primary and recurrent tumor populations.

TABLE 4
PATHOLOGICAL OBSERVATIONS IN PATIENTS WITH PRIMARY AND RECURRENT MENINGIOMAS

Observation	Primary	Recurrent	p Value
mitotic figures	22 %	44 %	<0.05
increased cellularity	13 %	28 %	NS (0.09)
brain invasion	6 %	11 %	NS
nuclear pleomorphism	25 %	28 %	NS
tumor necrosis	13 %	17 %	NS
aberrant nucleoli	19 %	33 %	NS
Ki-67 immunostaining	3.9 % (average)	5 % (average)	NS (0.21)
tumor type	30 benign 3 atypical 1 malignant	14 benign 6 atypical 1 malignant	<0.02

With regard to pathological observations (Table 4), the presence of mitotic figures was noted more commonly in recurrent (44%) compared with nonrecurrent (22%) tumors ($p < 0.05$). Increased cellularity was more common in recurrent lesions (28%) than in primary lesions (13%). The presence of brain invasion was as common in recurrent as nonrecurrent lesions (5% vs. 3%). Similarly, the presence of prominent nucleoli was noted more frequently in recurrent (33%) than in primary (19%) tumors. In addition, atypical and anaplastic tumors were more prevalent in the recurrent group than in the primary group (35% vs. 12%). There was virtually no difference in the incidence of nuclear pleomorphism or tumor necrosis when comparing primary and recurrent tumor groups. Although the Ki-67 labeling index was higher in the recurrent tumors (5% vs. 3.9%), this difference was not statistically significant.

DISCUSSION

Recurrent skull base meningiomas exhibit clinical, surgical, and pathological qualities that distinguish them from nonrecurrent skull base meningiomas. Each of the three broad areas of examination in this study: clinical signs and symptoms, surgical observations, and pathological observations, have been studied in recent years.

With regard to this specific series of patients, it should be noted that this was a retrospective study, and no attempt was made to match or stratify the primary and recurrent cohorts. Nevertheless, many of our findings were consistent with those noted in previous studies of recurrent and aggressive meningiomas.[28] For example, it was noted that a higher proportion of patients in the recurrent group were male (35% vs. 21%); however, this observation did not reach statistical significance.

Clinical signs and symptoms play an important role in the diagnosis of recurrent tumors. Symptom duration was found to be much shorter in patients with recurrent tumors (4.6 months) than in primary tumors (38 months) ($p < 0.05$). This observation may be explained by the increased vigilance in identifying relevant symptoms in patients who have undergone a previous tumor resection. However, it may also be explained by the increased aggressiveness of recurrent tumors. Certain clinical signs and symptoms, such as changes in visual acuity or the function of cranial nerves three, four, and six, were

thought to be more likely to be present in patients whose tumors were in specific locations such as the cavernous sinus. Therefore, the presence of these clinical signs and symptoms was stratified with respect to tumor location. As expected, patients with petroclival and petrous apex tumors do not commonly present with changes in visual acuity (0% of tumors), but do commonly present with cranial nerve three, four, and six symptoms (50% of tumors). Also as expected, patients with cavernous sinus tumors frequently present with cranial nerve three, four, and six symptoms (71% of tumors). However, patients with recurrent tumors in this location are unlikely to present with new cranial nerve three, four, and six symptoms (20% of tumors) if these findings had not improved following the initial surgical resection. These results are summarized in Table 5.

TABLE 5
STRATIFICATION OF THE PRESENCE OF ALTERATIONS IN VISUAL ACUITY OR CRANIAL NERVE THREE, FOUR, AND SIX FUNCTION WITH RESPECT TO TUMOR LOCATION

	Visual Acuity Symptoms		Cranial Nerve Symptoms	
Location	Primary Tumor (%)	Recurrent Tumor (%)	Primary Tumor (%)	Recurrent Tumor (%)
orbital	1 of 3 (33)	2 of 6 (33)	2 of 3 (67)	2 of 6 (33)
olfactory groove/subfrontal/planum	1 of 4 (25)	2 of 2 (100)	1 of 4 (25)	1 of 2 (50)
parasellar	4 of 6 (67)	2 of 6 (33)	0 of 6 (0)	0 of 2 (0)
cavernous sinus	3 of 7 (43)	2 of 5 (40)	5 of 7 (71)	1 of 5 (20)
sphenoid wing	3 of 4 (75)	2 of 2 (100)	1 of 4 (25)	1 of 2 (50)
petroclival petrous apex	0 of 10 (0)	0 of 3 (0)	5 of 10 (50)	0 of 3 (0)

Surgical observations appear to play an important role in the prediction of skull base meningioma recurrence. In our study, the intraoperative observation of muscle and bone invasion was noted more frequently in recurrent tumors (72%) than in primary tumors (38%) ($p < 0.05$). This may be due to the disruption of normal tissue planes or the inadvertent local seeding of tumor cells during the initial surgery, leading to muscle and bone invasion upon recurrence. Alternatively, the increased invasiveness of recurrent tumors may be caused by increased aggressiveness. As might be suspected, a subtotal surgical resection is more likely to lead to a tumor recurrence than a gross-total resection.[5,21,28] As a corollary, tumors in less accessible surgical sites, such as the skull base, were associated with a higher rate of recurrence.[27] However, in this study, there was no difference in the observed rate of gross-total resection between primary and recurrent tumors (21% vs. 22%).

Although there has been considerable investigation into the molecular biological behavior of meningiomas in recent years, no single test or group of tests has emerged to predict the potential for recurrence reliably. Traditionally, the Ki-67 labeling index has been cited as a predictor of tumor aggressiveness and recurrence.[6,15,16] However, other studies have demonstrated that high Ki-67 values may be present in tumors that have benign histology and behavior.[4,20] In our study, the Ki-67 labeling index was 3.9% for primary tumors and 5% for recurrent tumors, a difference that did not reach statistical significance, although not all specimens underwent Ki-67 analysis. However, an alternative measure of tumor aggressiveness and potential for recurrence may be the tumor type. Seven of 20 recurrent tumors were atypical or anaplastic, versus only four of 34 primary tumors ($p < 0.02$). Although cytogenetics were not evaluated in the current study, they have been previously investigated and recurrent meningiomas have been found to have a high incidence of complex karyotypes such as hypodiploidy and chromosomal structural rearrangements.[1,9,18,25]

The results of this study suggest that prognostic factors for skull base meningioma recurrence may be

unique in part due to their location and their propensity to invade muscle, bone, nerve, and the carotid artery. Further study of mechanisms of tumor invasion into skull base structures is warranted to forestall the incidence of recurrence in these locations.

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